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Lung: Short Report

Significance of Pulmonary Artery Dilatation in Lung Cancer Patients With Chronic Obstructive Pulmonary Disease Who Underwent Pulmonary Resection

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ABSTRACT

BACKGROUND The significance of pulmonary artery (PA) diameter in patients with non-small cell lung cancer (NSCLC) and chronic obstructive pulmonary disease (COPD) who undergo pulmonary resection has not been elucidated.

METHODS Data of 357 patients with NSCLC and COPD who underwent pulmonary resection were retrospectively reviewed. The main PA diameter, determined by preoperative computed tomography, relative to the body surface area (PBR), was used as an index of PA dilatation, and patients were divided into 2 groups using median values. The relationship between the PBR and short- and long-term outcomes was also analyzed.

RESULTS The mean age was 70.8 years, and 82% of the patients were men. The median main PA diameter was 24 mm (range, 17-43 mm), and the median PBR was 14.5 (range, 10.4-28.6). Lobectomy or more was performed in 276 patients (78%) and sublobar resection in 81 patients (22%). The postoperative complication rates did not differ between the low- and high-PBR groups (33% vs 32%, $P = .91$). The relapse-free survival (RFS) and overall survival (OS) rates of the low-PBR group were significantly better than those of the high-PBR group (5-year RFS: 76% vs 59%, $P = .0003$; 5-year OS: 88% vs 72%, $P = .0010$). A multivariable analysis identified high PBR as a poor prognostic factor for both RFS and OS.

CONCLUSIONS PA dilatation was associated with poor long-term outcomes and was an independent poor prognostic factor for both RFS and OS in NSCLC patients with COPD who underwent pulmonary resection.

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The number of patients with lung cancer and chronic obstructive pulmonary disease (COPD) is expected to increase. Mild-to-moderate pulmonary hypertension (PH) is a frequent complication of COPD. Pulmonary artery (PA) diameter measured using computed tomography (CT) can be used as an index of PH. In patients with COPD, PA dilatation by CT is associated with underlying PH and is also a predictor of exacerbation and death.[1] Recently, Eul and colleagues[2] reported that patients with lung cancer with PA dilatation had a worse prognosis than those

IN SHORT

- Pulmonary artery dilatation in non-small cell lung cancer patients with chronic obstructive pulmonary disease is associated with mild pulmonary hypertension.
- Pulmonary artery dilatation is associated with poor long-term outcomes and is an independent poor prognostic factor for both relapse-free survival and overall survival in non-small cell lung cancer patients with chronic obstructive pulmonary disease who undergo pulmonary resection.

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with narrower PAs. PA dilatation has been reported to be associated with postoperative complications in patients who undergo pulmonary resection.[3,4] However, the significance of the PA dilatation in non-small cell lung cancer (NSCLC) patients with COPD who undergo pulmonary resection has not been determined.

This study investigated the relationship between the main PA diameter measured using preoperative CT and short- and long-term outcomes in patients with COPD and NSCLC who underwent pulmonary resection.

PATIENTS AND METHODS

PATIENTS. The data of patients who underwent pulmonary resection for NSCLC between 2010 and 2019 at Osaka International Cancer Institute were retrospectively reviewed. Patients with a history of COPD who underwent curative pulmonary resection were included in this study.

METHODS. The Osaka International Cancer Institute Ethics Review Board approved the study protocol (control number: 22164). A thorough review of the patient records was conducted.

THE MEASUREMENT OF THE MAIN PA DIAMETER. All of the patients in this study underwent high-resolution CT within 60 days before pulmonary resection. The transverse axial diameter of the main PA at the level of the bifurcation of the right PA was measured using contrast-enhanced or plain CT, according to a previous report.[5] This study used the main PA-to-body surface area ratio (PBR) to compensate for physical differences.

STATISTICAL ANALYSES. Statistical analyses were performed using JMP Pro 17.0 (SAS Institute) and Stata 17 (StataCorp LLC) software. The data are expressed as mean ± SD or median values. The linear correlation between the 2 variables was measured using the Pearson correlation coefficient. The Student *t* test and the Fisher exact test were used to compare the 2 groups. The relapse-free survival (RFS) and overall survival (OS) rates after pulmonary resection were analyzed using the Kaplan-Meier method. Differences between groups were analyzed by the log-rank test, and a P value of $<.05$ was considered statistically significant. The RFS was defined as the time interval between the date of pulmonary resection and relapse or death or the last follow-up for live patients. OS was defined as the time interval between the date of pulmonary resection and death or the last follow-up for live patients. The Cox proportional hazards model was used to assess the effects of the covariates on OS and RFS. Statistical significance was set at $P < .05$. Factors with P values $<.05$ in the univariate analysis were used for the subsequent multivariable analysis.

Other methods are described in the Supplemental Methods.

RESULTS

The study enrolled 357 patients. The mean patient age was 70.8 years, and 82% were men. The distribution of the main PA diameter and PBR and the relationship between the PBR and pulmonary function are shown in Supplemental Figure 1. The median main PA diameter was 24 mm (range, 17-43 mm), and the median PBR was 14.5 (range, 10.4-28.6). The results of the preliminary analysis using the median value revealed that PBR is associated with the RFS. The ability of the PBR to predict the RFS was then evaluated using the area under the curve estimation method. The optimum cutoff value in this study was determined to be 14.28 (sensitivity, 67.03%; specificity, 51.88%; area under the curve, 0.5696). This value was used to divide patients into 2 groups in subsequent analyses: the low-PBR group (<14.28) and the high-PBR group (≥ 14.28).

Of the 357 patients, 256 (72%) underwent preoperative echocardiography. In the low-PBR group, 116 patients underwent echocardiography, and the estimated PA systolic pressure (ePASP) in 7 patients (6%) was ≥ 31 mm Hg. In contrast, 140 patients in the high-PBR group underwent echocardiography, and the ePASP in 19 patients (14%) was ≥ 31 mm Hg. The proportion of patients with ePASP ≥ 31 mm Hg in the high-PBR group tended to be higher than that in the low-PBR group ($P = .0607$). Patient characteristics according to the PBR groups are summarized in Supplemental Table 1. The age and ratio of women were both significantly higher in the high-PBR group than in the low-PBR group.

Operative and pathologic factors are summarized in Supplemental Table 2. Two patients (0.6%) died within 90 days of pulmonary resection. The histologic subtypes of adenocarcinomas in patients who underwent pulmonary resection after 2015 are summarized in Supplemental Table 3. The ratios of adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic-predominant adenocarcinoma were significantly higher in the low-PBR group than in the high-PBR group (32% [17 of 53] vs 12% [9 of 73], $P = .0131$).

Postoperative complications occurred in 115 patients (32%). The types of postoperative complications did not differ markedly between the low- and high-PBR groups, nor did the postoperative complication rates differ markedly between the groups (33% vs 32%, $P = .91$).

During the follow-up period, 91 patients died, including 52 of primary lung cancer and 39 of diseases other than primary lung cancer that was resected. The causes of death according to the PBR are summarized in Supplemental Table 4. The long-term outcomes of all patients according to PBR are shown in the Figure. The 5-year RFS rate for all patients was 68% and was significantly better in the low-PBR group than that of the high-PBR group (76% vs 61%, $P = .0005$). The 5-year OS

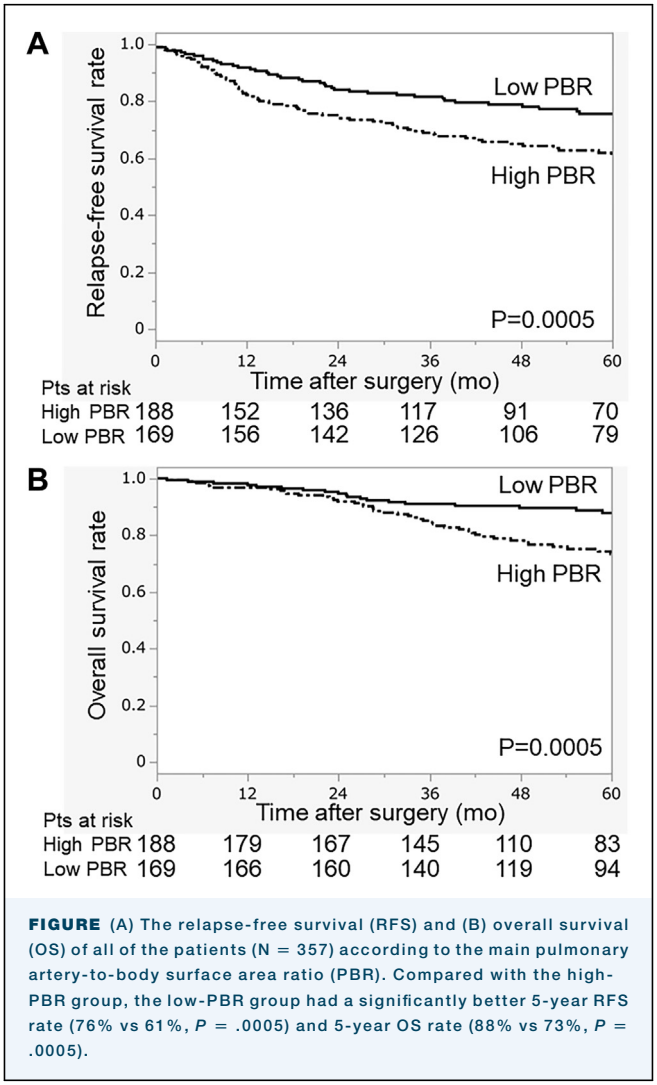

FIGURE (A) The relapse-free survival (RFS) and (B) overall survival (OS) of all of the patients (N = 357) according to the main pulmonary artery-to-body surface area ratio (PBR). Compared with the high-PBR group, the low-PBR group had a significantly better 5-year RFS rate (76% vs 61%, $P = .0005$) and 5-year OS rate (88% vs 73%, $P = .0005$).

rate of all patients was 80%, and was significantly better in the low-PBR group than that of the high-PBR group (88% vs 73%, $P = .0005$).

Univariate and multivariable analyses of factors influencing RFS after pulmonary resection are summarized in Supplemental Table 5 and Table 1, respectively. A multivariable analysis showed that high PBR and pStage II, III, or IV were poor prognostic factors for RFS. Univariate and multivariable analyses of the factors influencing OS after pulmonary resection are summarized in Supplemental Table 6 and Table 2, respectively. A multivariable analysis showed that age >70 years, a high PBR, pStage II, III, or IV, and a histologic type of nonadenocarcinoma were poor prognostic factors for OS.

TABLE 1 The Multivariable Analysis of Factors Influencing the Relapse-Free Survival After Pulmonary Resection

Factor	Hazard Ratio	95% CI	*P* Value
PBR (high/ low)	1.91	1.34-2.74	.0004
Carcinoembryonic antigen (ng/mL) (>5/≤5)	1.41	0.99-2.00	.0541
pStage (II, III, IV/I)	3.23	2.29-4.56	<.0001

PBR, main pulmonary artery-to-body surface area ratio.

Propensity score matching yielded 246 patients from the training cohort (123 in the low-PBR group and 123 in the high-PBR group). After propensity matching, the distribution of confounding variables was remarkably balanced between the high- and low-PBR groups (Supplemental Table 7). The long-term outcomes of cohort after propensity score matching, according to the PBR, are shown in Supplemental Figure 2. The RFS and OS of the low-PBR group were both significantly better than those of the high-PBR group, even after propensity score matching (5-year RFS rate: 86.69% vs 75.01%, $P = .003$; 5-year OS rate: 86.69% vs 71.16%, $P = .002$).

COMMENT

In this study, we investigated the association between the PBR and other clinical factors in patients with COPD and NSCLC who underwent pulmonary resection. The proportion of patients with mild PH (ePASP ≥31 mm Hg) in the high-PBR group tended to be higher than that in the low-PBR group. These data are in accordance with the report by Eul and colleagues,[2] in which ePASP and PA diameter had a significantly weak positive correlation ($R = 0.249$) in patients with lung cancer. For clinical factors, age, ratio of women, and ratio of atherosclerotic diseases were significantly higher in the high-PBR group than in the low-PBR group. The relationship between PA dilatation and age or atherosclerotic disease is in accordance with observations of a previous study.[5] Female predominance in PA dilatation may be influenced by both the predominance of mild PH in women and the method of setting the cutoff value of the PBR.

COPD presentation reportedly differs between the sexes, with women showing less frequent emphysema (loss of alveolar cells with increased air spaces) and more frequent airway obstruction (narrowing of the airways) than men.[6] Theoretically, continuous hypoxic pulmonary vasoconstriction in low-ventilation areas due to airway obstruction may decrease blood flow and cause PH with pulmonary vascular remodeling.

On the basis of these findings, women with COPD may be prone to mild PH. The distribution of the PA diameter reportedly differs between the sexes, and different cutoff values for each sex were set in a previous study.[5] The possibility remains that the optimal cutoff value of the PBR differs between the sexes.

TABLE 2 The Analysis of Factors Influencing the Overall Survival After Pulmonary Resection

Factor	Risk Ratio	95% CI	*P* Value
Age (>70/≤70)	1.78	1.15-2.75	.0099
Brinkman Index (>1000/≤1000)	1.52	0.99-2.34	.0539
PBR (high/low)	2.08	1.34-3.24	.0099
pStage (II, III, IV/I)	2.11	1.39-3.22	.0005
Histologic type (nonadenocarcinoma/ adenocarcinoma)	1.63	1.07-2.50	.0242

PBR, main pulmonary artery-to-body surface area ratio.

The present study demonstrated an association between PA diameter and long-term outcomes in patients with COPD and NSCLC who have undergone pulmonary resection. In terms of the cause of death, primary and nonprimary disease-related deaths both contributed to the difference in long-term outcomes between the low- and high-PBR groups. The difference in the number of primary disease-related deaths may be explained by the difference in the aggressiveness of the disease between the 2 groups. The subtype of adenocarcinoma has been reported to be associated with prognosis, as patients with adenocarcinoma in situ, minimally invasive adenocarcinoma, and lepidic-predominant adenocarcinoma have a good prognosis, whereas those with the micropapillary and solid subtypes have a poor prognosis.[7] In the present study, the ratio of subtypes with a good prognosis was significantly lower, whereas the ratio of those with a poor prognosis tended to be higher in the high-PBR group than in the low-PBR group.

In addition to this difference in the subtypes of adenocarcinoma, there is a possibility that lung cancer with advanced remodeling of the lung vasculature is more aggressive than that with less advanced remodeling. Pullamsetti and colleagues[8] observed increased vascular remodeling and perivascular inflammatory cell accumulation in human lung cancer tissues and demonstrated PH features in murine lung cancer models. They also demonstrated the possibility of nuclear factor-κB-driven chemokine generation in lung cancer cells for the accumulation of inflammatory cells. Because nuclear factor-κB signaling contributes to vascular remodeling as well as proliferation and angiogenesis in lung cancer, it is considered that lung cancer with a more aggressive character causes more severe PH.[9]

The difference in nonprimary disease death between the 2 groups is due to both death from pneumonia and other cancers. It is reasonable that pneumonia tens to be severe in patients with PA dilatation, because PA dilatation is reportedly associated with underlying PH and is also a predictor of acute exacerbation and death in patients with COPD.[1,10] In addition, there is a possibility that the chance of developing another cancer may be increased in patients in the high-PBR group, and/or the patients cannot tolerate standard treatments for another cancer; however, the precise explanation for this phenomenon must be explored in future studies. Based on our experience, we maintain that thoracic surgeons should not only conduct surveillance of lung cancer recurrence but also be alert for the development of pneumonia and other cancers in patients with PA dilatation in the postoperative follow-up period.

LIMITATIONS. Several limitations of the present study warrant mention. First, the study included patients who were treated during a 10-year period. Second, this was a single-center study.

CONCLUSION. PA dilatation measured using preoperative CT is associated with poor long-term outcomes and is an independent poor prognostic factor for both RFS and OS in NSCLC patients with COPD who undergo pulmonary resection.

The Supplemental Material can be viewed in the online version of this article [https://doi.org/10.1016/j.atssr.2024.03.001] on https://www.annalsthoracicsurgery.org

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